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Biological Activities of Artemisinins Beyond Anti-Malarial: a Review

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Abstract

Artemisinins, as a class of bioactive molecules, are mainly derived from the extracts of *Artemisia annua* L. and are the mainstay for malaria treatment, including severe malaria, uncomplicated malaria and multi-drug resistant malaria. They are well-known for their good tolerability, safety and rapid onset of action. Their efficacy is not only limited to malaria but also extends to a variety of human diseases such as cancer, tuberculosis, viral diseases (e.g. *Human cytomegalovirus*), immune diseases and parasitic infections like schistosomiasis. Being a cheap and safe drug class, which saves millions of lives at risk from malaria around the globe, can also have significant potential in oncology as they have shown anti-cancer properties in both cell lines and animal models. Active derivatives (e.g. artesunate, artemether and arteether etc.) have also been synthesized which can be used for oral, rectal, intramuscular and intravenous administration. A comprehensive update on the non-malarial use of artemisinins and/or their derivatives and artemisinin-based drug development beyond anti-malarial is discussed in this review. With the collaborative efforts in the clinical pharmacology of artemisinins and novel synthesis of artemisinin analogues, it is likely that artemisinin-based drugs will become an important armamentarium impeding a number of diseases beyond malaria.

Keywords Artemisinins · Derivatives · Biological functions · Infectious diseases

Introduction

Artemisinins are isolated from a Chinese medicinal annual herb *Artemisia annua* L commonly called as sweet wormwood (Asteraceae). Chemically it is a 1,2,-trioxane bearing an endoperoxide bridge. Professor You-you Tu and her research team isolated and discovered artemisinins and was awarded the Nobel Prize (2015) in Physiology and Medicine for this discovery (Tu 2011). Besides antimalarial properties, it has significant effects against different diseases such as cancer (Cheng et al. 2018), tuberculosis (Miller et al. 2011), autoimmune diseases (e.g. asthma, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), (Hou and Huang 2016) schistosomiasis (del Villar et al. 2012) and viral diseases (Efferth et al. 2008) and even against some plant tumors (Efferth 2017). Being a major global concern, malaria (a protozoan disease) with 214 million annual cases is the cause of 430,000 annual deaths most of whom are children younger than 5 years (Organization WH 2016). *Plasmodium* sp. particularly *Plasmodium falciparum* which is the causative agent of this fatal disease and proliferates in female *Anopheles* mosquitoes and can kill off the patients, usually in a matter of hours (Cox 2010). Some other species of the genus like *P. ovale*, *P. vivax, P. knowlesi* and *P. malariae* also cause malarial infections in humans (Wilson et al. 2011). Although, continuous efforts have been made since the 1940s to stop the outspread of the disease which was succeeded in North America, Europe, Canada and Russia (Alonso et al. 2011) and parts of Latin America and Asia (Carter and Mendis 2003) but not in Africa, particularly Sub-Saharan parts, where about 90% of malaria deaths take place and more than 80% of the annual patients are found with malaria (Lalloo et al. 2016). Prevalence has fallen up to some extent because

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of improved control, reasonable increases by funding agencies and enthusiasm for eradication and elimination (Sinka et al. 2012). Biting habits, density, longevity and efficiency of the vector are among the major determinants of the transmission intensity of malaria. With various measures such as insecticide-treated nets and vector control, research and development (R&D) have also initiated for new vaccine and drugs. While the most favoured therapy is the artemisinins combination therapy (ACT) (Yakasai et al. 2015) that is partially or completely based on artemisinins produced by the natural source (*Artemisia annua*) (Ikram et al. 2017). It is also possible to produce artemisinins in *Physcomitrella patens* and *Nicotiana benthamiana* heterologously (Han et al. 2016; Wang et al. 2016). The vaccine for *Plasmodium* is known as PfSPZ and can be obtained from *P. patens* and *N. benthamiana* (Rosales-Mendoza et al. 2017). Quinine as a first antimalarial drug was isolated from *Cinchona* bark and malaria has been mostly treated with drugs based on quinoline such as quinine, mefloquine and primaquine, chloroquine and antifolates. Unfortunately, many of the *P. falciparum* strains have developed resistance to chloroquine, halofantrine and mefloquine (Nondo et al. 2017). Interestingly, the bioactivity of artemisinins and/or their derivatives is not only restricted to malaria but have also shown activities against cancer both in vitro and in vivo. A number of case reports, usually, that of human cancer patients reveled that artemisinins have anti-cancer activities (e.g. breast cancer, abdominal ascites and hepatocellular carcinoma, lung cancer, brain cancer, prostate carcinoma and laryngeal squamous cell carcinoma etc.) (Konstat-Korzenny et al. 2018). Likewise malaria, tuberculosis is also lethal infectious and the most widespread disease around the globe (Hurtley et al. 2010). Presently, a huge number of the world population is infected with *Mycobacterium tuberculosis* which causes more than 2 million deaths around the globe per year (Bloom 1994). Although artemisinins itself are inactive against TB, but synergistically with a mycobacterial-specific siderophore analogue induces selective and significant activity against TB including *Mycobacterium tuberculosis* which is multi and highly drug-resistance strains (Zheng et al. 2017). Additionally, artemisinins and their semisynthetic derivatives' (e.g. Artesunate) bioactivity is even more broader and also includes the inhibition of certain viruses, particularly human cytomegalovirus and some members of the family *Herpesviridae* (Epstein-Barr virus and herpes simplex virus type 1) bovine viral diarrhea virus and hepatitis B and C virus (Hahn et al. 2018). Among the most common parasitic and prevalent diseases, schistosomiasis tends to be continue. In mid-2003 approximately 779 million people were at risk of this disease while the infected people were counted as 207 million (Ross et al. 2017). Trematode worm of the genus *Schistosoma* is the causative agent of schistosomiasis while 3 main species i.e. *S. japonicum*, *S. haematobium* and *S. mansoni* parasitize humans. Furthermore, some other species such as *S. intercalatum* and *S. malayensis* have also been found in Central Africa and Southeast Asia respectively (Pérez et al. 2012). In a large scale, although praziquantel is one of the most valuable and tested control strategy for schistosomiasis, however, the unavailability of therapeutic efficacy, particularly at early stages, is the limiting factor of paraziquantel and could be one of the main reasons for treatment failures. Hence, artemisinins and their derivatives emerged as a family of effective compounds and the best option with schistomicide activity (Crellen et al. 2016). Besides of artemisinins excellent clinical anti-cancer, anti-malarial and anti-tuberculosis effects, various studies also demonstrate that it has the potent anti-inflammatory and immune regulatory functions. Additionally, it has been reported that artesunate reduces the phagocytic index (in vivo) as well as peritoneal macrophages (Li et al. 2013a). Due to their eminent suppressive effects on both adaptive and innate immune cells, a number of experimental autoimmune models have been tested treating with artemisinin family drugs (Hou and Huang 2016). This review will mainly focus on artemisinins, their derivatives (especially synthetic) and artemisinin family drugs as a remedy for various diseases including cancer, malaria, tuberculosis and schistosomiasis.

Brief History and Discovery of Artemisinins

The discovery of artemisinins is somewhat linked with Vietnam War (1967) where Ho Chi Minh (the leader of North Vietnam) was at a war against the United States and South Vietnam. During the war, a majority of the Vietnamese soldiers who were trying to troop down the Ho trail suffered from malaria resistant to chloroquine. The leader asked Chinese Premier En-lai Zhou for assistance to provide some possible cure for his army against malaria (Ali et al. 2017). Meanwhile, malaria also emerged as a cause of hundreds to thousands of deaths in the Southern provinces of China. A meeting was scheduled under the instructions of Premier En-lai Zhou and Chinese Chairman Ze-dong Mao on May 23rd 1967 in China's capital city Beijing to consider the problem and prevent malaria parasites. In this regard, a program called Project 523 was set up involving more than 500 scientists from 60 different institutes. This project sets 2 goals: 1; short-term goal was to produce some anti-malarial drugs that could instantly be used by the soldiers in the battlefield, 2; the long-term goal of the concerned project was to develop new anti-malarial drugs by searching and screening recipes, synthetic chemicals and practices of traditional Chinese medicines (TCM) (Liu 2017). Initially, You-You Tu (a member of the Project 523) and her team visited

Hainan province of China where they studied patients infected with malaria (Miller and Su 2011). In 1969, she had an idea of screening of different Chinese herbs. Over 2000 traditional Chinese recipes were screened out by her team and made a total of 380 herbal extracts, which were first tested on mice infected with malaria (Krungkrai and Krungkrai 2016). A compound from *Artemisia annua* was more effective against "intermittent fevers" a hallmark of malaria. The preparation techniques were described in a 1600 years old book entitled "*The Handbook of Prescriptions for Emergency Treatments*" written by Hong Ge in 340. The book also recommends an amount of *A. annua* mixed thoroughly with water (usually 2 L), extract the juice and drink it all (Tu 2011). She extracted the compound using a low-temperature ether method and it was found completely effective in tests conducted on animals (mice and monkeys). She obtained artemisinins as a pure substance in 1972 and saved millions of lives. She was awarded the Lasker Award in clinical medicine and Nobel Prize in Medicine and Physiology in 2011 and 2015 respectively (Meskill 2017).

Physiochemical Properties of Artemisinins and their Derivatives

Chemical structure of the compound was determined by different approaches such as mass spectroscopy, spectrophotometry, X-ray crystallography and polyarithmetic analysis (Tu 2016). The chemical structure of artemisinins and their derivatives provided a base for further improvement of the drugs. Some chemical structures of artemisinins and their derivatives are given in Fig. 1. Physically, it is a white and needle-like crystals (without aromatic conjugate system) on 151–153 °C, insoluble in water but soluble in ether, acetone, petroleum ether, ethanol and alkali solution. The molecular formula is confirmed from fundamental analysis and mass spectra as $C_{15}H_{22}O_5$ (Guo 2016). Furthermore, due to their unique chemical structure and activity artemisinins can be kept without any decomposition at room temperature for a long time (Nakase et al. 2008). Qualitative analysis of the compound has shown positive color reactions by the oxidation of NaCI or NaOH while NaOH titration consumes one equivalent. It makes one equivalent of triphenylphosphine oxide by reaction

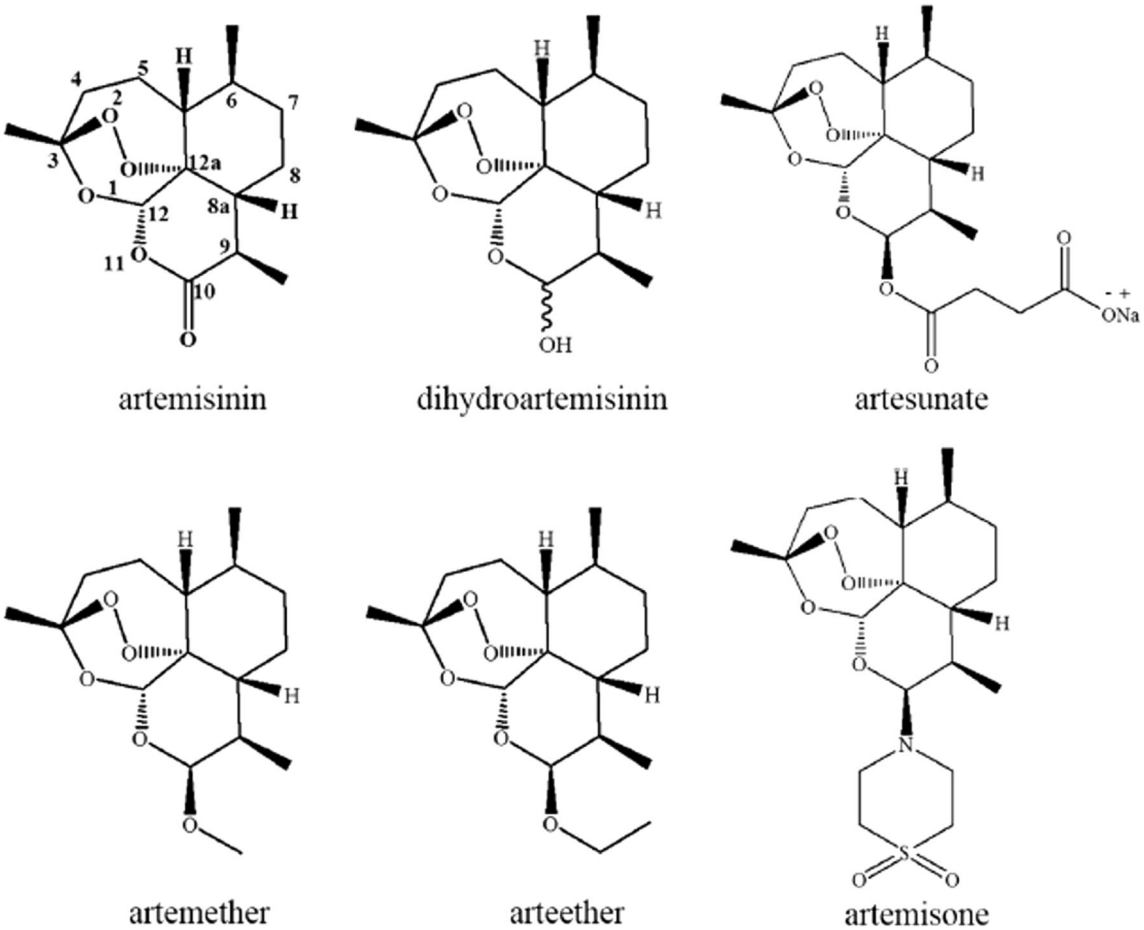

Fig. 1 Molecular Structures of artemisinin and its derivatives, (Reproduced from Ref. (Li et al. 2016), an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY))

with triphenyphosphine which indicate the presence of the oxidative group in its molecules. Several derivatives such as artesunate and artelinic acid (water soluble), artemether and arteether (lipid soluble) and dihydroartemisinin as an active metabolites are available to treat various diseases including malaria, cancer and tuberculosis (Liu 2017). In addition, a number of other sesquiterpenes are identified from ethereal extraction, including arteannuin A, B and C, and amorphane. Chemically, artemisinin is a 15-carbon sesquiterpene lactone with an endoperoxide (-C-O-C-O-) linkage and a molecular weight of 282 g/ mmol. This intact endoperoxide bridge is of immense importance and has a role in the formation of free radicles (Nakase et al. 2008). As artemisinin derivatives have no endoperoxide bridge and hence are devoid of anti-malarial activity. Furthermore, Fe (III) does not cause the reductive session of the endoperoxide as Fe (II) do. A series of semi-synthetic dihydroartemisinin (fluorinated) derivatives were patented by Centre National de la Recherche Scientifique in 2008 and named as monomeric artemisinin derivatives. These derivatives were exemplified by compounds 7–13 and metabolic stability was also imparted introducing a fluoro-alkyl substituent to C-10 position (Begue et al. 2008). In addition, by incorporating another functional group, mainly an ionizable, to such analogues at either C-16 or C-10 and water-soluble compounds were synthesized. Another group known as diametric artemisinins have been modified from parent artemisinin. In this group, 2 derivatives of monomeric artemisinin are coupled through different linkers connecting with C-10 positions. It is claimed that this group is more stable hydrolytically than other clinically used artemisinin such as artesunate (Blazquez et al. 2013).

Artemisinin Biosynthesis *in planta* (*A. annua*)

Although artemisinin biosynthesis has been investigated since long ago but the detailed regulation and biosynthesis is still not understood. Moreover, in-depth regulatory studies have been facilitated by the fact that biosynthesis as a whole is located in the glandular trichomes of *Artemisia annua* (Fig. 2) (Olofsson et al. 2011). A total of 3 molecules i.e. one dimethylallyl diphosphate (DMAAP) and two of isopentyl diphosphate (IPP), derived from the general terpenoid biosynthesis, are condensed by farnesyl diphosphate synthase (FPS) into farnesyl diphosphate (FPP, C15 sesquiterpenoid precursor) (Wen and Yu 2011). Interestingly, high artemisinin production has been obtained by the overexpression of FPS in *A. annua* (Banyai et al. 2010) which not only confirm the role FPS but also the availability of the substrate in artemisinin regulation and biosynthesis similar to that of other sesquiterpene lactones (Simonsen et al. 2013). By cyclization and carbocation formation, FPP is converted to amorpha-4, 11-diene by the enzyme amorpha-4, 11-diene synthase (ADS) (Wen and Yu 2011). In two further oxidization steps, in which, first amorpha-4, 11-diene is hydroxylated into artemisinic alcohol and then by the action of amorphadiene monooxygenase (an enzyme of cytochrome P450) oxidized to atremisinic aldehyde (Wang et al. 2011b). The activity of amorphadiene monooxygenase has confirmed via knock-out of the gene (endogenously) in the plant with no production of downstream products of amorphadiene (Czechowski et al. 2016). Likewise, another enzyme called alcohol dehydrogenase, which has latter been discovered, and has affinity towards artemisinin alcohol and further oxidizes it to aldehyde. The strong expression and specificity of alcohol dehydrogenase in glandular trichomes of *A. annua* confirms that this enzyme is responsible for artemisinic alcohol oxidation to artemisinic aldehyde (He et al. 2017). By the action of artemisinic aldehyde Δ 111 (13) reductase, artemisinic aldehyde reduced to another compound called dihydroartemisinic aldehyde and eventually oxidized by aldehyde dehydrogenase (an enzyme expressed mainly in the trichomes) to dihyroartemisinic acid (Liu et al. 2016). Aldehyde dehydrogenase not only catalyzing the oxidation of dihydroartemisinic aldehyde to the acid but also catalyzes the oxidation (a reaction catalyzed in yeast by amorphadiene monooxygenase) of artemisinic aldehyde to artemisinic acid (Teoh et al. 2009). In the second last step, an enzyme dihyroartemisinic aldehyde reductase changes dihydroartemisinic aldehyde to a “dead end” substance, dihydroartemisinic alcohol, which mainly affects artemisinin production (Kayser et al. 2011). The last step is a non-enzymatic and spontaneous (light-induced) reaction converting artemisinic acid to arteannuin B and dihydroartemisinic acid to artemisinin (Czechowski et al. 2016).

Pharmacological Activities/Effects of Artemisinins and/or their Derivatives

Artemisinin as an Effective Drug to Cure Malaria

Malaria is a parasite infection of red blood cells and caused by a unicellular protozoan parasite plasmodium mainly transmitted by anopheles mosquitoes. Being an endemic disease in several countries (approx 108) of Asia, South America and Africa etc. malaria is the cause of high mortality especially in children less than 5 years and the economic loss is huge in regions endemic with malaria (Stebbins et al. 2018). Although morbidity and mortality have decreased up to some extent but still it kills approximately 2000 people per day. Among strategies, two main factors account for these decreases: 1; insecticide-treated bed nets, 2; artemisinin combination treatments, as they are known for their good tolerability, rapid onset of action and safety. In addition to rapid tests, a valuable addition to microscopy for malaria diagnosis (White et al. 2013), effective treatment are also considered as the mainstay for malaria control (Shayo et al. 2015). An expert panel of the World Health

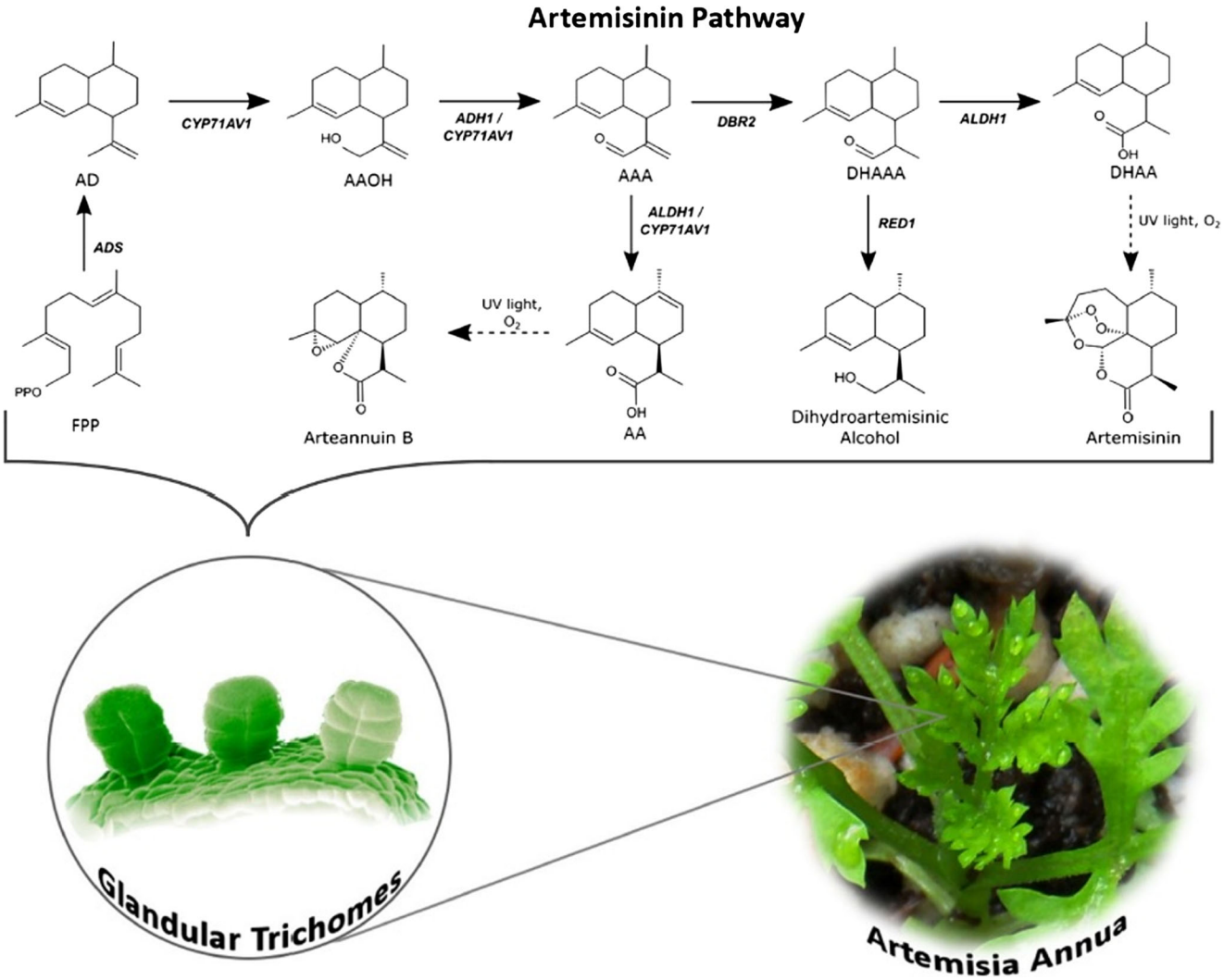

Fig. 2 Artemisinin biosynthesis pathway occurs in the glandular trichomes of *Artemisia annua* L. The pathway intermediates are defined as FPP, farnesyl diphosphate; AD, amorpha-4,11-diene; AAOH, artemisinic alcohol; AAA, artemisinic aldehyde; AA, artemisinic acid; DHAAA, dihydroartemisinic aldehyde; DHAA, dihydroartemisinic acid. Reproduced from Ref. (Ikram and Simonsen 2017), an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY))

Organization (2001) recommended the use of ACT for malaria treatment (Table 1) (Mandara et al. 2018). In large trials, parenteral artesunate (an artemisinin derivative) reduced severe malaria mortality by 22·5% in Africa and 34·7% in Asia compared with quinine, whereas adjunctive interventions have been uniformly unsuccessful (White et al. 2014). By 2006, ACT had become the most recommended treatment for malaria globally (Maxmen 2016; Wang et al. 2017a). Artemether-lumefantrine (Coartem®; Novartis) as a first ACT was validated by the US Food and Drug Administration (FDA) in April 2009 (Jiao et al. 2017). The most used combinition includes artesunate-sulfadoxine-pyrimethamine, pyronaridine-artesunate, arterolane-piperaquine, artemisinin-napthoquine, artesunate-amodiaquine, artemether-lumefantrine, DHA-piperaquine and artesunate-mefloquine (Premji 2009). To increase the efficacy and further ensure substantial treatment outcomes of ACT, caregiver and patient adherence, measurement methods (if they involved), associated factors and treatment guidelines is of immense importance (McCoy et al. 2017). According to WHO report (2009), ACT as the first-line remedy for malaria had adopted by less than 20 countries (Laxminarayan et al. 2006). Furthermore, with the cooperation of a number of donors including President's Malaria Initiative (PMI) and Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the number of countries that have established ACT has been further increased (Aregawi et al. 2009). In 2010, ACT was adopted by 84 countries, among them, 60 countries initiate to provide ACT free of cost (for all ages) in the public sector while 8 providing subsidized ACT via the Affordable Medicines Facility–malaria (AMFm) in the private sector (Committee WMPA and Secretariat 2012). A number of research and review articles, clinical trials and case reports have been evaluated the anti-malarial activities of artemisinins and their derivatives (Guo 2016; Wang et al. 2015).

Table 1 Artemisinin and/or its derivatives for the treatment of different diseases

Therapeutics	Drugs	Diseases/pathogens	Remarks	References
Anticancer	Artemisinin	Prostate cancer	In-vitro/In-vivo	(Morrissey et al. 2010)
	Artemisinin	Kidney cancer	In-vitro	(Kim et al. 2016)
	Artemisinin	Hepatocellular carcinoma	In-vitro	(Weifeng et al. 2011)
	Artemisinin	Ovary cancer	In-vitro/In-vivo	(Lai et al. 2013)
	Artemisinin	Colon cancer	In-vitro	(Leto et al. 2016)
	Artesunate	Cervical cancer	In-vitro/In-vivo	(Luo et al. 2014)
	Artesunate	Kaposi's sarcoma	In-vitro	(Thanaketpaisarn et al. 2011)
	Artesunate	Colorectal carcinoma	In-vitro	(Krishna et al. 2015)
	Artesunate	Melanoma	In-vitro	(Ramacher et al. 2009)
	Artesunate	Ovarian cancer	In-vivo	(Greenshields et al. 2017)
	Dihydroartemisinin	Breast cancer	In-vitro/In-vivo	(Ju et al. 2018)
	Dihydroartemisinin	Glioma	In-vitro	(Chen et al. 2015)
	Dihydroartemisinin	Gastric cancer	In-vitro	(Zhang et al. 2017)
	Dihydroartemisinin	Lung carcinoma	In-vitro/ In-vivo	(Zhou et al. 2010)
	Dihydroartemisinin	Leukemia	In-vitro	(Park et al. 2014)
	Dihydroartemisinin	osteosarcoma	In-vivo	(Ji et al. 2011)
Antiviral	Artemisinin	Hepatitis C virus	In-vivo	(Wohlfarth and Efferth 2009)
	Artemisinin	Bovine viral diarrhoea virus (BVDV)	In-vitro	(Blazquez et al. 2013)
	Artesunate	Herpes virus	In-vivo	(Hakacova et al. 2013)
	Artesunate	Hepatitis B virus	In-vitro/clinical	(Cui et al. 2010)
	Artesunate	Human cytomegalovirus (HCMV)	In-vitro/In-vivo	(Schnepf et al. 2011)
	Artemether	HCMV	In-vitro/In-vivo	(Barger-Kamate et al. 2016)
Antischistosomiasis	Artesunate	*Schistosoma haematobium*	In-vitro	(Keiser et al. 2010)
	Artemether	*Schistosoma mansoni*	In-vivo	(El-Lakkany and el-Din 2013)
	Praziquantel	*Schistosoma japonicum*	In-vivo	(Liang et al. 2011)
	Praziquantel	*Schistosoma mansoni*	In-vivo	(French et al. 2010)
	Praziquantel	*Schistosoma mekongi*	In-vitro/In-vivo	(Lovis et al. 2012)
Antituberculosis	Artemisinin	Tuberculosis	In-vitro/In-vivo	(Miller et al. 2011)
	Artesunate	Tuberculosis	In-vitro	(Choi 2017a)
Autoimmune diseases	Artemisinin	Endometriosis	In-vivo	(Wang et al. 2011a)
	Artemisinin	Lupus nephritis	In-vivo	(Wu et al. 2010)
	Artemisinin	Alzheimer's Disease	In-vivo	(Shi et al. 2013)
	Artesunate	Rheumatoid arthritis	In-vivo	(Li et al. 2013b)
	Artesunate	Systemic lupus erythematosus (SLE)	In-vivo	(Feng et al. 2017)
	Artesunate	Asthma	In-vivo	(Ho et al. 2012)
	Artesunate	Uveitis	In-vivo	(Wang et al. 2011a)
	Artesunate	Inflammatory bowel disease (IBD)	In-vivo	(Yang et al. 2012)
	Artemether	Rheumatoid arthritis	In-vivo	(Wu et al. 2018)
	Dihydroartemisinin	SLE	In-vivo	(YANG and ZHANG 2017)
	Dihydroartemisinin	Experimental autoimmune encephalomyelitis (EAE)	In-vivo	(Hou and Huang 2016)
Antimalarial	Artemether	Vivax malaria	Clinical	(Bassat 2011)
	Arteether	Cerebral malaria	In-vivo	(Ali et al. 2016)
	Artesunate	Vivax malaria	In-vivo	(Poravuth et al. 2011)
	Dihydroartemisinin	Vivax malaria	In-vivo	(Poespoprodjo et al. 2014)

Anti-Cancer Properties of Artemisinin

In the past two decades, besides from artemisinin's antipaludic activity, studies have evaluated the potential of both artemisinins and their various derivatives having inhibitory effects on the growth and particularly the proliferation of tumour cells (Chen et al. 2017; Jana et al. 2017). This specificity is because of certain characteristics of tumour cells, such that, susceptibility to reactive oxygen species (ROS), elevated the concentration of transferrin and iron and increased metabolism (Leto et al. 2016). High potency and specificity have also been shown by artemisinin tagged to certain transferrin through carbohydrate chain against cancer cells. In this regard, the conjugation is of significant importance, enables artemisinin delivery into cancer cells (Wong et al. 2017). Artemisinins and their derivatives inhibit cancer cell proliferation, yet with much lower efficiencies than their roles in killing malaria parasites (Zhang et al. 2016). In addition, due to its minimal toxicity and adverse effects, various case reports and clinical trials (conducted on humans and animals) have shown that artemisinin drug derivatives have promising in vitro and in vivo activity against certain types of cancer and used as antineoplastic drugs (Li 2012; Wang et al. 2017b). Intriguingly, artemisinin destroys only cancer cells by a mechanism called inducing apoptosis and is totally safe to normal cells (Wei et al. 2017). Dihydroartemisinin (an analogue of artemisinin discovered and developed in 1986) selectively killed cancer cells e.g. Molt-4 lymphoblastoid cells in vitro by co-incubation with holo-transferrin, while the same treatment was essentially non-toxic to normal human lymphocytes (Li et al. 2018). Furthermore, dihydroartemisinin and holotransferrin, as

a drug combination, was 100 times (LC50s of Molt-4 and normal lymphocytes were 2.6 μM and 230 μM, respectively) more effective compared with normal lymphocytes on Molt-4 cells (Kumari et al. 2017). Studies have been conducted to assess the in vivo anti-cancer bioactivity of artemisinin e.g. Moore et al. reported that the growth and proliferation of fibrosarcoma tumours in the rat was inhibited by oral administration of dihydroartemisinin along with ferrous sulphate (von Hagens et al. 2017). Artemisinin can induce a number of molecular pathways that may bring about apoptosis and necroptosis (Nakase et al. 2009). For instance, Hooft van Huijsduijnen concluded that artemisinin, dihydroartemisinin and artemisone induced apoptosis via the intrinsic pathway in the presence of caspase-3 and caspase-9 (Van Huijsduijnen et al. 2013). Another researcher, Tilaoui also showed that apoptosis is induced in vitro in murine mastocytoma cells (Tilaoui et al. 2014) while Zhang et al. exhibited that apoptosis is induced in human gastric cell lines and human esophageal cancer cells by artesunate (Liu et al. 2015). In a study conducted by National Cancer Institute with a number of cancer cell lines (to analyze their response in vitro to artesunate) concluded that cancer cells including ovary, kidney, melanoma cells, colon, prostate, central nervous system and breast showed susceptibility to the compound (Bai et al. 2018).

Artemisinin Potential as Anti-Tubercular Agent

Tuberculosis (TB) is among the most infectious diseases caused by a multidrug-resistant strains *Mycobacterium tuberculosis* while drugs such as rifampicin, pyrazinamide, isoniazid and ethambutol were thought to be the backbone of the current first-line treatment regimen (Organization WH 2011). This pathogen, which was responsible for the most deaths in 2014–2015, can persist for many years without causing any disease symptoms in the host (Zheng et al. 2017). After *M tuberculosis* emergence as resistant-strains to first and second-line drugs (Skrahina et al. 2011) e.g. viomycin, D-cycloserine and cephalosporin, and further restricted access to second-line drugs for the proper treatment, it's time for an urgent action (Falzon et al. 2013). Furthermore, long course treatment is among the basic challenges of the present TB therapy. In this regard, drugs with shortening the course of therapy can revolutionize TB control (Leistikow et al. 2010). The spread and development of extensively drug-resistant (XRD) and multi-drug resistant (MDR) strains of *M tuberculosis* have accelerated research activities around the globe (Rojas Vargas et al. 2016). Consequentially, the pipeline has expanded for potential and new drugs (Makarov et al. 2009), but no fully effective drug against TB has been marketed (Harper 2007). Besides, potent anti-malarial activity, artemisinin (as a conjugate of mycobactin-artemisinin) has potential and profound activity against TB. Although artemisinin itself is inactive against TB, but synergistically with an analogue induces selective and significant activity against TB pathogen (Wencewicz and Miller 2017). Notably, a number of studies have been shown that when artemisinin as a mycobactin-artemisinin conjugate is delivered into *M tuberculosis*, it causes the burst of reactive oxygen through Fenton reactions and kills *M tuberculosis*. In addition, whole-cell and physiochemical studies indicated that the iron complex of the conjugation reduces from ferric-to-ferrous which initiates radical chemistry, particularly Fenton-type, with artemisinin component (Liu et al. 2018). The anti-*M tuberculosis* activity of artesunate was shown in an experiment by Won Hyung Choi via different selective anti-*M tuberculosis* various assays such as Ogawa slant medium assay, MGIT 960 assay and Resazurin Microtiter (REMA) assay while artemisinin effect was found low as compared to artesunate. Additionally, with a single dose for 21 days, artesunate showed persistent effects and anti-*M tuberculosis* activity as they inhibit pathogen growth and proliferation in vitro. Artesunate also revealed activity against TB in vivo for four weeks (daily dose of 3.5 mg/kg) with no induce toxicity or side effects (Choi 2017b).

Artemisinin-Based Drugs against Schistosomiasis

In spite of continuing control efforts, schistosomiasis is still the major health problem of tropical and subtropical countries. The causative agent for this infectious disease is *Schistosoma*, a parasitic trematode worms, retains mainly in the mesenteric portal system of the host. Besides negative effects on pregnancy outcome, child development and agricultural production (Adenowo et al. 2015) this debilitating and chronic disease is a cause of labour loss and emerge as a big threat to the economy (Ross et al. 2017). In 2008, the number of people treated for schistosomiasis was 17.5 million globally while 11.7 million out of total belongs to sub-Saharan Africa. Although, some countries including Tunisia and Japan has been eradicated it successfully, whereas, Morocco and some countries of Caribbean Island have already made a good progress on management and control of schistosomiasis (Utzinger et al. 2009). China, Egypt and Brazil initiates for its elimination whilst a number of countries, particularly the sub-Saharan region, are still facing problems with schistosomiasis (Jones et al. 2018). According to WHO the disease accounts for more than 40% of tropical disease. Several drugs such as praziquantel, metrifonate and oxamniquine etc. have been used for the treatment of the disease, while among them praziquantel becomes the first-line drug. However, in the recent past, the resistance of the pathogen to praziquantel has come into concern, that may further necessitate struggle for some substitutes (Tambo et al. 2014). Although, praziquantel is more active against *schistosomes* in the adult stage but with high rates of re-infection and lack of therapeutic efficacy (against early stage) are the main limitations of praziquantel (Vale et al. 2017). Thus, being versatile

pharmacological tools in nature, artemisinin derivatives like artesunate and artemether have a potential against schistosomiasis which was described for the first time in the1980s in China. In 1996, artemisinin derivatives were approved for the prevention of schistosomiasis by Chinese Ministry of Health (Doenhoff et al. 2008). Furthermore, they are active against a number of *schistosome* species such as *S. mansonai*, *S. japonicum* and *S. haematobium* by targeting schistosomulum (Liu et al. 2017). Artesunate-sulfamethoxypyrazine plus pyrimethamine, artesunate-sulfadoxine-pyrimethamine and artesunate-amodiaquine have been tested on children infected with *S. haematobium* (Shuhua et al. 2002).

Anti-Viral Activities of Artemisinin

In addition to its antimalarial, antiangiotensin, anti-inflammatory, antibacterial, and anticancer activity artemisinins and their synthetic derivatives especially artesunate has impressive and relatively broad antiviral activity against hepatitis B (HBV), human cytomegalovirus (HCMV) and Bovine Viral Diarrhea Virus (BVDV) (Morere et al. 2015). The remarkable anti-cancer activity of artemisinin compounds have already been confirmed as they demonstrated the potential antiviral efficacy by applying a concept called chemical hybridization (Fröhlich et al. 2017a, b). It has been reported that artesunate has potential inhibitory effects against herpes viruses like human herpes viruses 6A (HHC-6a), herpes simplex virus 1 (HSV-1) and Epstein-Barr virus. In neonates, patients with transplant recipients and AIDS, human CMV is the main cause of infection (Schreiber et al. 2009). The so far available antiviral drugs such as cidofovir, foscarnet and ganciclovir (mainstream anti-CMV) prevent the elongation of viral DNA by targeting activity of viral DNA polymerase but they have a number of side effects including the emergence of drug resistance and bone marrow suppression (Schreiber et al. 2009). With a profile of high safety and tolerability, the intensive use of artesunate has been demonstrated in malaria patients (Zhang et al. 2018). Fortunately, due to its multi-functionality, the value of the compound is not only restricted to malaria but has also been suggested as a substitute to already available antiviral drugs, particularly, in patients with failing therapy (Kar Han Lau et al. 2011). In addition, it can be used orally, intravenously, intramuscularly and also through the rectal route (Morris et al. 2011). Hence, as the best option, artesunate demonstrate its anti-CMV effects by inhibiting the transactivation of DNA-binding factors Sp1 and NF-κB (Kadambari et al. 2017). Furthermore, artesunate has also inhibitory effects against HBV replication by suppressing surface antigen secretion of HBV, as a result, decrease HBV-DNA levels in vitro (Qi et al. 2013) while in vivo it undergoes a rapid conversion by cellular and plasmatic esterases into dihydroartemisinin (an active metabolite) (Fröhlich et al. 2017a, b). Additionally, pharmacological interest has been increased in the recent past in artemisinin in order to treat viral diseases due to severe limitations of the available antiviral therapy (Sayce et al. 2016). Artesusnate activity is not limited to laboratory strains but it has a prominent effect against clinical isolate mutants with a strong resistance against various conventional antiviral drugs (Durantel et al. 2004). Different sensitivities were shown by herpesviruses analyzed by Kaptein SJ et al. to artemisinin and artesunate; as artemisinin was found with poor and no activity against HCMV and human herpes virus 6A respectively while artesunate was found with strong antiherpsviral potency (Kaptein et al. 2006).

Artemisinin Drugs for the Treatment of Autoimmune Diseases

Autoimmune diseases, a family of about 80 illnesses, mainly share a common pathogenesis in which the body attack (also called immune-mediated attack) on its own cells, tissues and organs. They have highly variable manifestations and can affect any site in the body and are most common in industrialized societies (Schwartz et al. 2016). Diseases of this family often disabling and most of the times leading to complete or partial loss of organ function. Being a threat to public health globally, the prevalence of autoimmune diseases is the common problem of both developing as well as developed countries (Bellone 2010). Since cures for most of the autoimmune diseases are not available and usually patients, particularly women in child-bearing years, face debilitating illness with costly treatment (Pagan et al. 2018). Beyond antimalarial agent, artemisinins and their related derivatives have immunoregulatory effects on immune cells such as splenocytes, neutrophils, T-cells, B-cells and macrophages (Yi et al. 2017). Artemisinin-based combination therapies may depress neutrophils as they kill different microbes. Furthermore, artemisinin with semi-synthetic derivatives may also interfere with the most functional competencies of neutrophils (Wang et al. 2008). Additionally, artemisinin can reduce the secretion level of tumor necrosis factor (TNF) in vivo, and have been shown a strong inhibitory effect towards TNF-α in vitro release from macrophage. They have been found to modulate host immune functions mediated by macrophage by interrupting transcriptional signaling pathways in macrophages (Loop and Pahl 2003). The effect of artemisinin is not only restricted to drop-off in cytokines release from macrophage but it also downregulate nitric oxide production, which is important for macrophage-mediated immune reactions (Wang et al. 2009). Artesunate, dihydroartemisinin, artemether and SM905 (a new derivative) have shown protective effects against rheumatoid arthritis (Li et al. 2013b). Among these, artesunate was found resistant to cartilage and bone diseases and development of tissue edema in experimental models, mediated by the suppression of a number of pro-inflammatory cytokines like granulocyte macrophage colony stimulating factor (GM-CSF), TNF- α, interleukin (IL-6), IL-17 α, IL-8 and IL-1β through

inhibition of the phosphoinositide 3-kinase (P13K/Akt), mitogen-activated protein kinase and NF- κB signaling pathways (Li et al. 2013b). A series of new artemisinin derivatives (SM735, SM905, SM933 and SM934) with immunosuppressive functions against T cell activation in vitro has been synthesized in the recent past (Ho et al. 2014).

Concluding Remarks and Future Recommendations

Being a class of bioactive molecules, artemisinins and their derivatives have a number of biological activities beyond antimalarial (severe malaria, uncomplicated malaria and multidrug resistant malaria), that includes anti-schistosomal, anticancer, anti-viral, anti-tuberculosis and anti-immune diseases (Table 1). In addition, they are also becoming established as anti-parasitic, anti-fungal, anti-allergic and anti-protozoal agents. The potential of artemisinin lies in broader antidisease applications, especially in addressing a tough challenge posed by certain advanced cancers for which more expensive but less effective treatments are available. Furthermore, questions related to safety and long-term use, dosing regimens and particularly interactions, which may be positive or negative, with already available therapies and toxicities (which might be associated to the treatment of different tumours) should be answered by clinical studies on urgent bases to consider drugs like artesunate for oncological indications. Also, the next landmark in research regarding artemisinin will be to further analyze the potential efficacy of novel analogues in various disease models beyond malaria which includes immune disorders and infectious diseases. Although, there is extensive preclinical data (both in vitro and in vivo) in the literatures which supports a number of therapeutic applications for artemisinin, particularly artesunate, in human diseases. However, apart from a well-established safety background for artemisinin, clinical studies about artesunate related non-malaria-diseases are still very limited. With the collaborative efforts in the clinical pharmacology of artemisinin and novel synthesis of artemisinin analogues, it seems that artemisinin based drugs will become an important armamentarium impeding a number of diseases beyond malaria.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interest to claim.

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